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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/151,409	09/10/1998	JAMES B. DALE	481112.410	7693

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EXAMINER
DEVI, SARVAMANGALA J N

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 07/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/151,409	Dale
Examiner	**Art Unit**
S. Devi, Ph.D.	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 16, 2003*.

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *12, 15-17, 19, 21, 23, 27, 30-32, 34, 36-38, 40, 42, 44, and 54-69* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *12, 15-17, 19, 21, 23, 27, 30-32, 34, 36-38, 40, 42, 44 and 54-69* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☒ Interview Summary (PTO-413) Paper No(s). *36.*
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

RESPONSE TO APPLICANT'S AMENDMENT

Applicant's Amendment

1) Acknowledgment is made of Applicant's amendment filed 04/16/03 (paper no. 37) in response to the non-final Office Action mailed 01/17/03 (paper no. 35). With this, Applicant has amended the specification.

Status of Claims

2) Claims 12, 16, 17, 19, 23, 27, 32, 36-38, 40, 42, 44, 54, 56 and 58 have been amended via the amendment filed 04/16/03.

New claims 59-69 have been added via the amendment filed 04/16/03.

Claims 12, 15-17, 19, 21, 23, 27, 30-32, 34, 36-38, 40, 42, 44 and 54-69 are pending and are under examination.

Prior Citation of Title 35 Sections

3) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

4) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection(s) Withdrawn

5) The objection to the specification made in paragraph 5 of the Office Action mailed 01/17/03 (paper no. 35) is withdrawn in light of Applicants' amendment to the specification.

Rejection(s) Withdrawn

6) The rejection of claims 12, 15, 27 and 36 made in paragraph 12 of the Office Action mailed 01/17/03 (paper no. 35) under 35 U.S.C. § 102(b) as being anticipated by Mori *et al.* (*Pediatr. Res.* 39: 336-342, February 1996) as evidenced by Fischetti *et al.* (US 5,985,654) or Vashishstha *et al.* (*J. Immunol.* 150: 4693-4701, May 1993, already of record), is withdrawn in light of Applicants' amendment to the claims and/or the base claim(s).

7) The rejection of claims 27, 30, 32 and 34 made in paragraph 13 of the Office Action mailed 01/17/03 (paper no. 35) under 35 U.S.C. § 103(a) as being unpatentable over Mori *et al.* (*Pediatr.*

Res. 39: 336-342, February 1996) in combination with Pillai *et al.* (US 5,334,379, already of record), is withdrawn in light of Applicants' amendment to the claims and/or the base claim(s).

8) The rejection of claims 27, 30, 32 and 34 made in paragraph 14 of the Office Action mailed 01/17/03 (paper no. 35) under 35 U.S.C. § 103(a) as being unpatentable over Mori *et al.* (*Pediatr. Res.* 39: 336-342, February 1996) in combination with Pillai *et al.* (US 5,334,379, already of record), is withdrawn in light of Applicants' amendment to the claims and/or the base claim(s).

New Rejection(s)

Applicant is asked to note the following new rejection(s) made in this Office. The new rejections are necessitated by Applicant's amendments to the claims and/or the base claims and submission of new claims.

Rejection(s) under 35 U.S.C § 112, Second Paragraph

9) Claims 12, 15-17, 19, 21, 23, 27, 30-32, 34, 36-38, 40, 42, 44 and 54-69 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite, for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

(a) Claims 12 and 27 are confusing and/or lack antecedent basis for the recitation 'at least one immunogenic polypeptide' in part (b) of the claims (see line 9 of claim 12; and line 11 of claim 27). Claims 12 and 27, as amended, include two different 'portions': 'an amino terminal portion' of a Group A streptococcal M protein, and a 'multivalent immunogenic portion'. The open claim language 'comprising' or 'comprises' allows inclusion of 'immunogenic polypeptides' that are and that are not from the amino-terminal portion of a Group A streptococcal M protein within the claimed fusion polypeptide. It is not clear whether the above-identified 'at least one immunogenic polypeptide' is from the amino-terminal portion or non-amino terminal portion of a Group A streptococcal M protein. Clarification/correction is requested.

(b) Claims 16, 37 and 56, as amended currently, and the new claim 61, are confusing and/or lack antecedent basis in the recitation: '.... immunogenic polypeptides'. The source of these immunogenic polypeptides is unclear. Are these non-M protein polypeptides, or polypeptides from the carboxy-terminal of Group A streptococcal M protein? Clarification/correction is requested.

(c) Claims 55, 57, 60 and 62 is vague, indefinite and confusing in the limitation 'according to claim ... wherein each M protein portion', because the amended base claim 16 or 27,

from which claims 55, 57, 60 and 62 depend directly or indirectly, does not recite any 'M protein portion'. The instant claims are further improperly broadening in scope with regard to the recitation 'each M protein portion', because the recitation 'an amino-terminal portion of a Group A streptococcal M protein' in the amended base claim 12 or 27 is much narrower in scope than the broader recitation in claims 55, 57, 60 and 62: 'each M protein portion'. Since an 'M protein portion' comprises both 'an amino-terminal portion' and 'a carboxy-terminal portion', it is unclear what is encompassed in the recitation, 'each M protein portion'. Does this 'M protein portion' contain a carboxy-terminal or amino-terminal portion of a Group A streptococcal M protein, alone or in combination with a part each other? Is this 'M protein portion' 'comprised' within the 'immunogenic portion' or outside the 'immunogenic portion'? Clarification/correction is requested.

(d) Claims 15, 17, 19, 21, 23, 30-32, 34, 36, 38, 40, 42, 44 and 54-69, which depend directly or indirectly from claim 12 or 27, are also rejected as being indefinite because of the indefiniteness identified above in the base claim(s).

Rejection(s) under 35 U.S.C § 112, First Paragraph

10) Claims 12, 27 and those that depend from these claims are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Base claims 12 and 27, as amended, include the recitation: "the carboxy-terminal polypeptide is a reiteration of 'at least one' immunogenic polypeptide from the amino terminal of the immunogenic portion and 'is at the carboxy-terminal' of the fusion polypeptide". The term 'at least one' is equivalent to any number that exceeds one. However, there appears to be no descriptive support within the instant specification, as originally filed, for a recombinant fusion polypeptide wherein 'more than one' immunogenic polypeptides from the amino-terminal of the immunogenic portion are present 'at the carboxy-terminal of the fusion polypeptide', as recited currently. At line 19 of page 18 and in Figure 1 of the specification, the descriptive support is for '**a** reiterated immunogenic polypeptide ... included at the end of the vaccine', but not for more than one such reiterated immunogenic polypeptide at the carboxy-terminal of the fusion polypeptide [Emphasis added]. Therefore, the above-identified limitation(s) in the claims is considered to be new matter. *In*

re Rasmussen, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicant is respectfully requested to point to the descriptive support in the specification as filed, for the newly added limitation(s), or to remove the new matter from the claim(s).

11) Claims 12, 27 and those that depend from these claims are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Base claims 12 and 27, as amended, exclude the limitation 'comprising at least 10 amino acids' and include the recitation: "at least two immunogenic polypeptides from Group A streptococcal M protein, the polypeptides being an amino-terminal portion of a Group A streptococcal M protein and being capable of eliciting an immune response against Group A Streptococci'. As amended, the 'at least two immunogenic polypeptides' from an amino-terminal portion of a Group A streptococcal M protein can be of any length, i.e., less than 10 amino acids-long. However, there is no descriptive support in the specification, as originally filed, for a recombinant fusion polypeptide comprising at least two immunogenic polypeptides from an amino-terminal portion of a Group A streptococcal M protein which are less than ten amino acids in length. All through the specification, including at page 2, lines 8-11 and lines 21-23; page 5, lines 13-15; abstract, lines 2-4; and the original claim 1, the descriptive support exists only for 'at least two immunogenic polypeptides from a Group A streptococci of at least 10 amino acids in length which are capable of stimulating an immune response against Group A streptococci .....'. Therefore, the above-identified limitation(s) in the claims is considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicant is respectfully requested to point to the descriptive support in the specification as filed, for the newly added limitation(s), or to remove the new matter from the claim(s).

12) Claims 12, 27 and those that depend from these claims are rejected under 35 U.S.C. § 112,

first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

New claims 64 and 67 include the recitation: 'a marker amino acid sequence'. New claims 65 and 68 include the recitation: 'the marker amino acid sequence or inconsequential non-immunogenic polypeptide ... capable of binding a nickel resin'. New claims 66 and 69 include the limitation: 'joined by amino acids 'encoded' by a restriction enzyme site'. Applicants point to page 8, lines 14-20; page 9, lines 1-13; page 17, lines 11-13; and Example 2, particularly at page 16, lines 24-26 of the specification as providing descriptive support for the new claims. However, there is no descriptive support in the instant specification, as originally filed, for the limitations: 'a marker amino acid sequence'; amino acids 'encoded' by a restriction enzyme site; and 'the marker amino acid sequence or inconsequential non-immunogenic polypeptide ... capable of binding a nickel resin'. The description at lines 24-26 on page 16 states:

> PBS and lysed in a French pressure cell at 1000 psi. The hexavalent protein was purified from the supernatant using Ni-NTA resin according to the protocol provided by the manufacturer (Qiagen). The elution buffer containing the protein was ...

and does not associate the recited 'marker amino acid sequence' or the 'inconsequential non-immunogenic polypeptide' with the 'capability to bind a nickel resin'. Therefore, the above-identified limitation(s) in the claims is considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicant is respectfully requested to point to the descriptive support in the specification as filed, for the newly added limitation(s), or to remove the new matter from the claim(s).

Claim(s) Interpretation

13) The differing scope or meaning of the recitation in part (a) of the base claims: 'the polypeptides being an *amino-terminal portion of a Group A streptococcal M protein*' and the recitation in part (b) of the base claims: 'at least one immunogenic polypeptide from the *amino-terminal of the immunogenic portion*' has been noted. It is further noted that due to the absence of

proper antecedence, the recitation, 'at least one immunogenic polypeptide' in part (b) of the base claims is merely required to be from 'the *amino-terminal of the immunogenic portion*', but is not required to be one of 'the' two immunogenic polypeptides recited in part (a) of the claims, wherein at least two of the immunogenic polypeptides of the immunogenic portion are required to be from *an amino-terminal portion of a Group A streptococcal M protein*. Because of the open claim language used in the claims, 'at least one immunogenic polypeptide from the amino-terminal of the immunogenic portion' as recited in part (b) of the claims is not required to be the amino terminal portion of a Group A streptococcal M protein, but can be any immunogenic polypeptide including one other than an amino terminal polypeptide of a Group A streptococcal M protein.

It is further noted that the base claims, as amended, do not require the size of the immunogenic polypeptides to be at least 10 amino acid-long, but encompass those that are less than 10 amino acids in length. For example, a less than 10 amino acid-long immunogenic N-terminal M24 polypeptide repeated two times in a recombinant fusion polypeptide, as long as the second copy is at the C-terminal of the fusion polypeptide (for example, -M24-M6-M24 or M24-X-M24 fusion polypeptide) and another immunogenic polypeptide from a different M serotype, or a different non-M protein polypeptide is 'comprised' within the immunogenic portion, would anticipate the claimed product. Some of the various possible fusion polypeptides currently encompassed in the scope of the base claims, which include the open claim language 'comprising' and 'comprises', are illustrated below. The highlighted (bold) polypeptide, M19 or non-M protein polypeptide X, represents the C-terminal polypeptide of part (b) of the claims, whereas the shaded polypeptides represent the 'multivalent immunogenic portion' and/or 'at least two immunogenic polypeptides' of part (a) of the base claims. The unshaded and non-highlighted polypeptides represent any immunogenic or non-immunogenic polypeptides that are not a part of the 'immunogenic portion', but are 'comprised' within the claimed fusion polypeptide.

X-M19-M19-M19

M24-M24-M24-M5-M5-M5-M6-M6-**M6-M19-M19-M19**

X-M19-M19-X-X-X-X-X-X-**M19**

M19-X-X-X-X-**M19**-X-X-X-X-X-X-X-**M19**

M19-X-X-X-X-**M19**-X-X-X-X-X-X-**X**

The second fusion polypeptide illustrated above is taught by Dale *et al.* ('421) as explained below under the art rejection(s). The same is also taught by Dale *et al.* (US 6,063,386).

Rejection(s) under 35 U.S.C. § 102

16 37 56

14) Claims 12, 15, 17, 19, 21, 23, 27, 30, 31, 36, 38, 40, 42, 44, 54, 58, 59 and 63-69 are rejected under 35 U.S.C. § 102(b) as being anticipated by Dale *et al.* (WO 94/06421, already of record) ('421).

Instant claims include the open claim language, such as, fusion polypeptide "comprising" and immunogenic portion "comprises". The transitional limitations "having" or "comprising", similar to the limitations such as, "including," "containing," or "characterized by," represent open-ended claim language and therefore, do not exclude additional, unrecited elements. See MPEP 2111.03 [R-1]. See *Moleculon Research Corp. v. CBS, Inc., 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986)*; *In re Baxter, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981)*; *Ex parte Davis, 80 USPQ 448, 450 (Bd. App. 1948)* ("comprising" leaves "the claim open for the inclusion of unspecified ingredients even in major amounts"). Therefore, the limitation "comprising", "comprises" or "includes" in the instant claims allows additional amino acid residues to be present on one or either side of the immunogenic polypeptides; additional immunogenic polypeptides or amino acids to be present on one or either side of the immunogenic portion and/or in between the two immunogenic polypeptides in the immunogenic portion.

Dale *et al.* ('421) disclosed a recombinant fusion or hybrid polypeptide comprising at least two immunogenic peptides, at least ten amino acid-long, capable of eliciting an immune response against group A streptococcal infections. A vaccine comprising a recombinant multivalent hybrid M protein vaccine is taught for use against multiple serotypes of group A streptococci. The vaccine contains epitopes or antigenic determinants (i.e., immunogenic polypeptides) that evoke opsonic antibodies against multiple serotypes of group A streptococci (see page 8, last paragraph), including serotypes 1, 3, 5, 6, 14, 18, 24, 27, 29 or others (see page 9, third full paragraph; see claims, especially claims 1-16). The multivalent hybrid M protein is made by recombinant DNA technology (see page 9, lines 1 and 2). The multivalent construct contains one or more repeats of any particular amino terminal fragment of different serotypes and is capable of eliciting the desired opsonic antibodies against the multiple serotypes of Group A streptococci (see page 9, last sentence and first

full paragraph). The hybrid protein has the amino terminal amino acid fragment to contain 1 or more amino terminal portions of streptococcal serotypes 1, 3, 18, 27 and/or 29. The hybrids of the prior art are constructed to contain one or more fragments of the amino terminal region of serotypes known to have or not to have a rheumatogenic effect (see paragraph bridging pages 25 and 26). The immunogenic recombinant multivalent M protein comprising amino terminal fragments of the streptococcal M protein elicits opsonic antibodies against multiple serotypes of Group A streptococci and does not elicit tissue cross-reactive antibodies (see claims 2 and 1). The hybrid construct contains NH2-terminal regions which raise not only opsonic responses, but protective mucosal responses. The carboxy terminal fragment is not always necessary for a hybrid to raise mucosal or cellular responses (see page 27, second full paragraph). Hexavalent and decavalent hybrid M proteins are taught (see page 28). Hybrid M proteins include amino acids of the amino termini of the M proteins, i.e., M24, M5, M6 and M19, or types 1, 3, 18, 27 and/or 29 or any other presently known or to be discovered serotypes (see paragraph bridging pages 25 and 26). A therapeutic composition comprising a pharmaceutically acceptable carrier and recombinant multivalent hybrid M proteins is taught. The hybrid polypeptide may be injected to a mammal in an appropriate biologically acceptable diluent or in complete or incomplete Freund's adjuvant (see page 11, second paragraph; page 36, third full paragraph; and page 37, first full paragraph). The immunogenic portions contain 15 amino acid units (see page 13, lines 1-2). The polyvalent or hybrid M proteins contained in phosphate buffered saline and complete Freund's adjuvant are used to immunize rabbits. The use of a mixture or cocktail of such hybrid proteins is taught (see page 23, middle paragraph). Dale *et al.* ('421) disclosed recombinant hybrid polypeptides comprising repeated (i.e., reiterated) amino acid fractions of different serotypes of group A streptococci, for example, M24-M24-M24-M5-M5-M5-M6-M6-**M6-M19-M19-M19** multivalent hybrid (see page 27, fourth full paragraph), wherein the **M6-M19-M19** (shadowed part above) is viewed as the multivalent immunogenic portion recited in part (a) of the base claims, and the third **M19** unit (bold) is viewed as the reiterated 'at least one immunogenic polypeptide from the amino terminal of the immunogenic portion' serving as the C-terminal polypeptide of the whole fusion construct, M24-M24-M24-M5-M5-M5-M6-M6-**M6-M19-M19-M19**, as recited in part (b) of the base claims (see also below). The hybrid construct illustrated in Figure 7 contains 15 amino acid subunits repeated three times and can contain individual

repeated segments longer or shorter than 15 amino acids (see page 27, paragraphs 3-5). The M protein fragments of the fusion polypeptide taught by Dale *et al.* ('421) are linked by amino acids specified by the restriction enzyme sites, BamH1, Sal 1 and Nco1 (see Figure 7; paragraph bridging pages 19 and 20; and page 28), or a poly-G clamp (see page 22, lines 9-13; and page 18, first full paragraph). Multimeric amino-terminal fragments of *emm* genes repeated three times and joined with restriction enzyme sites and a poly-G-clamp were constructed using PCR amplification (see page 22). Dale *et al.* ('421) taught vaccines that include amino acid subunits of any or all of the 1 through 80 different serotypes known (i.e., inclusive of serotypes 11, 13, 22 and 28) or to be discovered (see page 34, second paragraph).

The prior art multivalent recombinant fusion polypeptide taught in Figure 7, '(SUBUNIT VAR)', clearly meets the product claimed in the base claims, which are the broadest independent claims. The prior art fusion construct taught in Figure 7 is a multivalent recombinant fusion polypeptide since it contains M protein fragments from more than one serotype, i.e., M24, M5,M6 and M19. It includes a multivalent immunogenic portion comprising the minimum 'at least two immunogenic polypeptides' as recited, for example:

Arg Val Phe Pro Arg Gly Thr Val Glu Asn Pro Asp Lys Ala Arg (M6) Pro Trp ***Arg Val Arg Tyr Thr Arg His Thr Pro Glu Asp Lys Leu Lys Lys*** **(M19) Arg Val Arg Tyr Thr Arg His Thr Pro Glu Asp Lys Leu Lys Lys** (M19).

The shaded portion constitutes the 'multivalent immunogenic portion' as recited in part (a) of the base claims. When the third reiterated copy of the M19 fragment (bold M19) is added to the above-identified immunogenic portion at its C-terminal end as depicted in Figure 7, it meets the recombinant fusion polypeptide claimed in the base claims, as shown in Figure 7 and herebelow:

.....(M24).....(M5).. **Arg Val Phe Pro Arg Gly Thr Val Glu Asn Pro Asp Lys Ala Arg** (M6) Pro Trp **Arg Val Arg Tyr Thr Arg His Thr Pro Glu Asp Lys Leu Lys Lys (M19) Arg Val Arg Tyr Thr Arg His Thr Pro Glu Asp Lys Leu Lys Lys** (M19) **Arg Val Arg Tyr Thr Arg His Thr Pro Glu Asp Lys Leu Lys Lys** (M19).

The underlined amino acid sequence is viewed as the marker amino acid sequence or the inconsequential non-immunogenic polypeptide. The last highlighted (i.e., bold) reiterated M19 polypeptide from the amino terminal of the shaded immunogenic portion meets the limitation in part

(b) of claims 12 and 27: "a carboxy-terminal polypeptide that protects the immunogenicity of the immunogenic portion, wherein the carboxy-terminal polypeptide is a reiteration of at least one immunogenic polypeptide from the amino terminal of the immunogenic portion and is at the carboxy-terminal of the fusion polypeptide". The rest of the M24 and M5 polypeptide repeats that are present in the fusion polypeptide of Dale's Figure 7 are viewed as the immunogenic or non-immunogenic Group A streptococcal M polypeptides 'comprised' within the fusion polypeptide, or outside the immunogenic portion.

Claims 12, 15, 17, 19, 21, 23, 27, 30, 31, 36, 38, 40, 42, 44, 54, 58, 59 and 63-69 are anticipated by Dale *et al.* ('421).

Rejection(s) under 35 U.S.C. § 103

15) Claims 27, 32 and 34 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Dale *et al.* (WO 94/06421, already of record) ('421) in combination with Pillai *et al.* (US 5,334,379, already of record).

The teachings of Dale *et al.* ('421) are described above which do not disclose their composition further comprising a immunomodulatory cofactor, such as, IL-2, IL-4 or IFN-gamma.

However, Pillai *et al.* disclosed that cytokines and lymphokines, such as, interferons, IL-2 and IL-4, are the modulators of the immune response, and that these modulators augment proliferation and differentiation of antigen or mitogen stimulated T cells. Cytokines and lymphokines are taught to have adjuvant activity with the capacity to enhance the immune response to an antigen (see column 1, lines 11-39). Pillai *et al.* further taught that cytokines and lymphokines "help evoke a protective immune response against marginally or non-immunogenic conjugated antigens, and bound unconjugated antigens" (see paragraph bridging columns 6 and 7).

It would have *prima facie* been obvious to one of ordinary skill in the art at the time the invention was made to add Pillai's IL-2 or IL-4 to Dale's ('421) composition comprising the fusion M polypeptide, to produce the composition of the instant invention with a reasonable expectation of success, because Pillai *et al.* explicitly taught that the recited cytokines have immune-enhancing adjuvant activity and the ability to evoke a protective immune response to the antigen present. One of skill in the art would have been motivated to produce the instant invention for the expected benefit of producing a fusion M polypeptide vaccine composition having enhanced immunogenicity, since

such vaccine compositions are ideally desired in the art of vaccines.

Claims 27, 32 and 34 are *prima facie* obvious over the prior art of record.

Suggestions

16) The following amendments are suggested for Applicant's consideration:

(a) To be consistent with the claim language used in claims 12 and 27, it is suggested that Applicant replace the recitation 'Streptococcal' with --streptococcal -- in claims 55, 57, 60 and 62.

(b) To be consistent with the claim language used in claims 55, 57, 60 and 62, it is suggested that Applicant replaced the recitation 'a Group A Streptococci serotype' with --a Group A streptococcal serotype-- in claims 15 and 36.

(c) For clarity and for the purpose of distinctly claiming the subject matter, in claims 17, 19, 21, 23, 38, 40, 42 and 44, it is suggested that Applicant replace the recitation 'from a serotype ... Group A Streptococci' with --from Group A streptococcal serotype ...--.

(d) Instant claims are drawn to a fusion polypeptide and recite polypeptides of differing scope or length: 'fusion polypeptide'; 'immunogenic polypeptides' and 'C-terminal polypeptide'. For clarity and for the purpose of distinctly claiming the subject matter of the invention, it is suggested that Applicant amend the first line of all claims directly or indirectly dependent from claim 12 by replacing the recitation: 'The polypeptide of claim ...' with --The fusion polypeptide of claim ...-- thereby distinguishing the fusion polypeptide from the rest of the recited polypeptides.

Relevant Prior Art

17) The prior art made of record and not currently relied upon in any rejection is considered pertinent to Applicants' disclosure:

- Dale *et al.* (US 6,063,386, filed 09/16/1992 - already of record) taught the recombinant hybrid polypeptides comprising group A streptococcal amino terminal M protein fragments similar or identical to that taught by Dale *et al.* (WO 94/06421).

Remarks

18) Claims 12, 15-17, 19, 21, 23, 27, 30-32, 34, 36-38, 40, 42, 44 and 54-69 stand rejected.

19) Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

20) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone number is (703) 308-4242, which is able to receive transmissions 24 hours a day and 7 days a week. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

21) Any inquiry concerning this communication or earlier communication(s) from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. A message may be left on the Examiner's voice mail service. The Examiner can normally be reached on Monday to Friday from 7.15 a.m to 4.15 p.m. except one day each bi-week which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

July, 2003

S. DEVI, PH.D.
PRIMARY EXAMINER